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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GAMETT, DANIEL C	

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1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/079,929	SPERANDIO ET AL.	
	Examiner	Art Unit	
	DANIEL C. GAMETT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-17* is/are pending in the application.

4a) Of the above claim(s) *1-3 and 7-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,6 and 11-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/31/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/2007 has been entered. Claim 5 is cancelled. Claims 1-3 and 7-10 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Claims 4, 6 and 11-17 are under examination.

2. All prior objection/rejections not specifically maintained in this office action are hereby withdrawn.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 4, 6 and 11-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting cell death by contacting a cell with SP600125, does not reasonably provide enablement for any method that requires exclusively inhibiting paraptotic as opposed to apoptotic cell death or any method that requires prior knowledge that the target cells are undergoing paraptosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The courts have interpreted the first

paragraph of 35 U.S.C. 112 to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. Each of these factors has been addressed on the record; the pertinent matters will be reiterated with reference to Applicant's remarks. The instant disclosure fails to meet the enablement requirement for the following reasons:

a. *The nature of the invention:* Claims 4 and 6 are drawn to a method of inhibiting paraptotic cell death in a mammalian neural cell comprising contacting said cell with an effective amount of JNK inhibitor SP600125. Claims 11-17 are drawn to methods of treating a condition associated with excessive cell death in vivo.

b. *The breadth of the claims:* The cell recited in claim 4 is a neural cell, which is understood to mean a neuron or glial cell. In claim 6, the cell is a human cell. Claims 11

and 12 are drawn to treatment of any neurodegenerative of ischemic condition; claims 13-15 recite only ischemic condition and claims 16-17 recite neurodegenerative condition.

c. The state of the prior art and the predictability or lack thereof in the art: At the time of invention, the term "paraptosis" was newly coined; the cytological and biochemical differences between paraptosis and apoptosis were only beginning to be appreciated. The two forms of programmed cell death can be stimulated by the same stimuli (specification p. 6 lines 3-5: "Receptors involved in mediating cell death may activate either the paraptotic or apoptotic pathway, or may activate both pathways.") and can be inhibited by the same inhibitors (specification p. 6 lines 25-29: "inhibitors or neutralizing agents of the Jun N-terminal kinases (JNKs) … block both the paraptotic and the apoptotic cell death pathways."). It was known that apoptosis may or may not require JNK activity in different situations, depending on the nature of the cell death signal (Sabapathy et al 1999, Curr Biol. 1999 Feb 11; 9(3):116-25; of record) and it was not known whether paraptosis would be similarly variable. Under those circumstances, a skilled artisan can only tell by experimentation whether (a) paraptosis will occur and (b) SP600125 inhibits said paraptosis, in any particular system. With regard to *in vivo* use and the treatment of specific conditions, it is noted that there a conditions wherein "non-apoptotic" programmed cell death is suspected to occur (see specification p.1, line 26-p.2 line 14). It remains unknown whether any of these instances of cell death represent paraptosis as defined by applicant, and the extent to which these non-apoptotic events are dependent upon JNK activity also remains unknown. Nevertheless, JNK activity has been

known to be important in the recited pathological conditions. For example, Borsello, Current Pharmaceutical Design, 2007, 13: 1875-1886 (of record on IDS filed 10/31/2007) cite several pre-filing date references pointing to a role of JNK in Alzheimer's disease (at least refs. 31-33, 35, 36) and Parkinson's disease (at least refs. 84, 88, 89). Therefore, the prior art suggests that inhibitors of JNK activity should be beneficial to inhibit cell death and in treatment of neurodegenerative diseases. These benefits would be expected for any JNK-dependent mechanism, be it paraptosis or apoptosis.

d. The amount of direction or guidance present and the presence or absence of working examples: Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). The evidence that SP 600125 can inhibit paraptosis in any cells is indirect, being based on the observation "antisense oligonucleotide constructs for JNKI or JNK2 were able to inhibit IGFIR-IC induced paraptosis in 293T cells" (on p.38, lines 9-14). This information does not provide enablement for the use of SP600125 because oligonucleotides target the mRNA for JNK whereas the SP600125 targets the enzyme. At best, these asserted results merely provide a basis for a hypothetical prediction that SP600125 is capable of inhibiting paraptosis in a model system. Furthermore, 293T cells are not neural cells. With regard to *in vivo* use, the specification does not establish that paraptosis as defined by applicant is actually involved in any condition or, if so, the paraptotic program involved is dependent upon JNK activity and so may be inhibited by SP600125. The specification offers no guidance as to critical matters that would enable treatments, such as patient

selection, dosage, and the unpredictability that is inherent in extrapolating from a cell culture model to a complex system such as a diseased mammal.

e. *The quantity of experimentation needed:* In order to avoid inherent anticipation by any prior administration of SP600125 to a patient population displaying a neurodegenerative or ischemic condition, the instant claims should recite how the administration of SP600125 targets paraptosis as opposed to apoptosis or any other JNK-dependent process that may be occurring. For example, it may eventually be learned that a particular target of treatment does not undergo any JNK-dependent apoptosis. In order to practice the invention the skilled artisan would need to perform experimentation to first determine whether SP600125 is indeed capable of inhibiting paraptosis in any cell, then specifically a neural cell. Then, the artisan could begin to move from tissue culture models to *in vivo* treatments. The artisan would need to perform the extensive experimentation necessary to establish a connection between specific *in vivo* conditions, paraptosis, and JNK activity. This would establish *why* to attempt to use SP 600125 for treatments, not *how* to use it. All of this amounts to undue experimentation, not routine development. The courts have stated that patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be patentable. Tossing out the mere germ of an idea does not constitute an enabling disclosure. Reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. See *Genentech v. Novo Nordick A/S* (CAFC) 42 USPQ2d 1001 (1997).

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 4, 6, 11, and 13-17 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 7119114 (Bennett), filed August 18. 2000. Patent 7119114 is granted from the US Patent Application published as 20040072888 which was cited in the rejection of record. Therefore, the reasons of record regarding Application 20040072888 are maintained and hereby extended to include new claim 17. Applicant's arguments filed 10/31/2007 have been fully considered but they are not persuasive. As stated in the prior office actions, Bennett teaches that SP600125 inhibits JNK and inhibits cell death, and further teaches the use of SP600125 for treatment of human conditions involving programmed cell death; these conditions include those recited in new claim 17, as well as those recited in the original claims (column 5, lines 1-10). Applicants argue that Bennett discusses methods of using pyrazolone derivatives for treating a laundry list of diseases, but that SP600125 is not specified explicitly as being used to treat these diseases. Applicants further argue that given the number of R groups and the substitutions that are taught in the specification, one of skill in the art would not be able to pick out one of possibly hundreds or thousands of derivatives from this generic group and match it with the long list of

conditions recited. With regard to the "laundry list" is noted that Applicants' own assertion of support for the instant claims relies on a similar teaching of multiple conditions (instant specification, page 14, lines 23-27; page 15, lines 2-3). Furthermore, Bennett did not fail to lead one of skill in the art to pick SP600125 out of thousands of derivatives and match it with the list of conditions. Bennett demonstrated an *in vivo* effect of SP600125 in a model of neurotoxicity that involves cell death. Specifically, the example in Bennett at column 39, lines 45-65, shows that "Compound I" protects rats from kainate-induced seizures. The structure of Compound I is shown in column 7, lines 38-54; it is identical to SP600125 (see also Fig. 1 of Bennett *et al*, Proc. Nat. Acad. Sci. (USA) vol.98, no.24, Nov. 20, 2001, of record). Therefore, Bennett contacted a mammalian neural cell with an effective amount of SP600125. The instant claims are not distinguished over Bennett because they require only one active step: contacting a mammalian neural cell with SP6100125. "Inhibiting paraptotic cell death" and "treating a neurodegenerative or ischemic condition" are expressions of purpose and intended result recited in the preambles and in "wherein" clauses in the independent claims. Such expressions are non-limiting, since language does not result in manipulative difference in steps of claims. See *Bristol-Myers Squibb Co. v. Ben Venue Labs Inc.*, 246 F.3d 1368, 58 USPQ2d 1508 (Fed. Cir. 2001) (61 PTCJ 623, 4/27/01), where a patent for administering the anti-cancer drug paclitaxel was anticipated by a scientific article describing the same method but with no anti-tumor response. That court held that expressions of anti-tumor efficacy did not distinguish the claimed method from the prior art. The court further held that preamble language in claims of patents directed to administration of anticancer drug are expressions of purpose and intended result, and as such are non-limiting, since language does not result in manipulative difference in steps of claims. See

also, *Minton v. Nat'l Ass'n of Securities Dealers, Inc.*, 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003)): a "'whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.'"

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 7119114 (Bennett) as applied claims 4 and 11 above, in further view of Shultz *et al.*, Annals of Neurology. 1999 Apr;45(4):421-429, US Patent 7018988, filed March 20, 2001 and US Patent Application Publication 20030139406, filed October 16, 2001.

9. Claim 12 is drawn to the method of claim 11 wherein the administered SP600125 is part of a combination therapy that further comprises a compound known to inhibit apoptosis. As noted, Bennett teaches administration of SP600125 for the purpose of inhibiting cell death. Bennett, however does not specifically teach a combination therapy as required by claim 12. The obviousness of combining SP600125 with a compound known to inhibit apoptosis does not rely on appreciation that SP600125 can inhibit paraptosis. In Bennett, SP600125 is presented as an inhibitor of JNK-dependent cell death. Apoptosis is a complex process and JNK is far from the only molecule that may be targeted to inhibit apoptosis. For examples, Shultz *et al.* teach inhibition of caspases (several caspase inhibitors are listed in table 2); US 7018988 teaches

inhibition of Bax activity (see Abstract); and US 20030139406 teaches inhibition of PDE4 [0438]. It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re* Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Conclusion

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, PhD., whose telephone number is (571)272-1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571 272 0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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DCG
Art Unit 1647
4 January 2008

/David S Romeo/
Primary Examiner, Art Unit 1647